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The neonatal significance of selected perinatal events among infants of low birthweight – III. Follow-up studies

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In prior reports, the early neonatal implications of selected perinatal events among infants of low birth weight were reviewed [1, 2]. Factors potentially having an influence upon neonatal mortality were surveyed, utilizing an entire three-year experience of babies weighing less than 2001 gm at birth in a large university teaching hospital. It was found that, as expected, birthweight and gestational age had a major impact upon neonatal survival; but maternal hypertension, as well as prolonged ruptured membranes with babies weighing less than 1200 gm or with gestational ages less than 30 weeks had a salutary effect upon the likelihood of survival. Babies of very low birthweight born after premature labor or with isoimmunization were disadvantaged when compared to the population as a whole. The effect of compounding of neonatal complications upon survival was investigated, and it was found that babies experiencing a host of adverse events were more likely to fail to survive than those with relatively uncomplicated courses, when considered by birthweight and gestational age.

Survivors weighing less than 1500 gm at birth from this study period (July, 1973 – June, 1976) were entered into the long-term follow-up study program existing for many years within the University of Colorado Neonatal Division. Results of these investigations upon survivors persisting in the system from 6 to over 30 months are the subject of this report.

1 Materials and methods

The original study involved 330 mothers, cared for at Colorado General Hospital, who delivered 356 live-born infants weighing less than 2001 gm. The records on one additional mother and 5 babies could not be made available for review. The birthweight distribution, including survivals through the period of the original study, is listed in Tab. I.

The follow-up program enrolled only babies weighing less than 1500 gm at birth. Tab. II lists survivors weighing 500–1500 gm available for the project. Excluded from these studies were 8 post-neonatal deaths, as well as those with anomalies, congenital chronic infections, chromosomal abnormalities, and 17 babies who were lost to ultimate contact by the system, but who were alive and well by reports from elsewhere.

Of those originally weighing 500–900 gm, 5 survivors were available for assessment. This

Tab. I. Survivors of original study period

	Born		Survived	
Weight (gm)	No.	% total births	No.	% birthweight
501– 900	47	13.3	12	26.1
901–1200	47	15.9	42	73.7
1201–1500	74	20.7	62	84.9
1505–2000	180	50.2	170	94.4

Tab. II. Survivors weighing 500–1500 gm in follow-up studies

Weight (gm)	No.	(% born)	(% first report [1])
500– 900	5	(10.6)	(41.7)
901–1200	31	(54.5)	(73.8)
1201–1500	42	(56.8)	(67.7)

Excludes 8 post-neonatal deaths; anomalies; congenital infections (chronic); karyopathies; those lost to follow-up. Total survivors = 108. Reviewed here = 78.

Distribution of neurologic abnormalities by type and magnitude.

Weight (gm)	Mental Abnormality	Motor Abnormality	Overall* (% normal)
500– 900	3/5	4/5	1- 3- 1- 5 (20)
901–1200	6/29	16/30	14- 6-11-31 (45)
1201–1500	8/41	16/42	23-10- 9-42 (55)

Not all babies could be assessed by all testing parameters.

* Normal-mild deficit-moderate or severe deficit-total.

represented 10.6% of the original live-born group, and 41.7% of those covered in our initial reports [1, 2]. Of those 901–1200 gm, 31 (54.4% of those born and 73.8% of those previously reported) were studied. In the weight group 1201–1500 gm, 42 babies were assessed, representing 56.8% of those born and 67.7% of those initially reported. In all, there were 108 survivors of the original group of 181 children in these birthweight categories, of whom 78 long-term outcomes are reported.

Tab. II also reviews the frequencies and distribution of severity of detected neurologic deficits in the population followed, utilizing liberal criteria for abnormality.

Children were assessed by the Denver Developmental Screening Test [3] and/or BAYLEY scales [4] for mental and motor handicap. For purposes of analysis, babies were scored as normal (including those judged only borderline abnormal and expected to resolve) and abnormal (from moderate to severe). In addition, an overall score was given to summarize their status, based upon a subjective impression of their degree of handicap. This score ranged from 0 (normal) to 3 (severely affected). These three scoring systems were separately subjected to simple correlations with 44 maternal-fetal factors (see Tab. III) and 26 neonatal categories (see Tab. IV) in all three categories by continuity-corrected chi-square analysis of FISHER's Exact Test using the Statistical Analysis System. Any perinatal event found to show a potential correlation, with a null hypothesis probability of 0.20 or less, was added to the data base for further analysis, in order to determine those factors having the most substantial controlling influence upon outcome. All factors in any two of the three birthweight categories achieving this qualification for analysis were included in the third, even if a lesser

Tab. III. Variables examined for association with handicap

Maternal-Fetal		
Maternal age	Breech	Abruptio
Race	HBP – 1st TM	Fetal transfusion
Parity	HBP – 2nd TM	LFT abnormal
Prior preg. (#)	HBP – 3rd TM	Labor induction
Prior abortions (#)	HBP – labor	Duration, ruptured membranes
Family history HBP	HBP – postpartum	GA by dates
Personal history HBP	L/S ratio	GA by exam
Spontaneous rupture of membranes	Uric acid	APGAR 1 minute
	Creatinine clearance	APGAR 5 minutes
Bleeding	Cesarean delivery	Gender
Premature labor	Fetal distress	Labor tolerance
Fever	Rapid delivery	Delivery mode
Rh sensitized	Infection	Alcohol (labor suppression)
HBP on admission	Previa	Apresoline
Referred	Meconium	Magnesium sulfate

HBP = high blood pressure; TM = trimester; LFT = liver function tests; GA = gestational age; # = number.

Tab. IV. Variables examined for association with subsequent handicap

Neonatal		
Resp. distress	? sepsis	(Exchange transfusion)
Hyaline membrane disease	Anemia	Hospital stay
Hyperbilirubinemia	Apnea/bradycardia	(Thrombocytopenia)
Hypocalcemia	Seizures	Necrotizing enterocolitis
Hypotension	(Pulmonary hemorrhage)	SGA by dates
Hyponatremia	Air leaks	SGA by exam
Hypoglycemia	Disseminated intravascular coagulation	R Index
Late Acidosis	Intracranial hemorrhage	M Index
Patent ductus arteriosus	Anomaly	

( ) = numbers too small for meaningful analysis; SGA = small for gestational age (≤ 10th percentile); R Index = Respiratory Index (see [1]); M Index = Morbidity Index (see [1]).

Tab. V. Variables selected for subsequent analysis

Motor deficit	
Spontaneous reptured membranes	(APGAR 1)
Referred (*)	APGAR 5
Breech	Resp. distress (*)
Abruptio (*)	Hypocalcemia
Maternal age	Hyponatremia
Race	Hypoglycemia
HBP on admission	Patent ductus arteriosus
(–) Family history HBP	Apnea/bradycardia
(–) HBP – 3rd TM	Hypotension
(–) HBP – PP (*)	Anemia
Parity	Necrotizing enterocolitis
GA by dates	(Anomaly)
Rapid delivery (*)	(M Index)
Meconium (*)	(R/O) sepsis)
(Labor intolerance)	

Variables in parentheses added for interest; significant in other categories
(–) = removed for inadequate numbers
(*) = statistically significant by χ^2; at "p" less than 0.05.
HBP = high blood pressure; TM = trimester; PP = postpartum; GA = gestational age; R/O = rule out.

Tab. VI. Variables selected for subsequent analysis

Mental deficit	
Maternal age	Resp. distress
Race	Hyaline membrane disease
Spontaneous ruptured membranes	Hypocalcemia
GA by dates	Hypotension
Labor intolerance	Patent ductus arteriosus (*)
Meconium	Anomaly
Family history HBP	R Index
(Abruptio)	M Index
(Parity)	(Hypoglycemia)
(Rapid Delivery)	R/O sepsis
APGAR 1	Thrombocytopenia
(APGAR 5)	

(*) = statistically significant (at < 0.05); (–) = removed for inadequate numbers; ( ) = added for interest; significant in other categories.

degree of impact was found in the other birthweight category. The categories selected for stepwise discriminant analysis are included in Tabs. V–VII.

2 Results

Tabs. VIII and IX list antepartal and neonatal factors selected as having a potentially significant influence (either beneficial or detrimental) upon long-term outcome in two or more outcome categories. Factors indicated by the (+) appeared to have had a beneficial effect upon outcome, in that their occurrence was associated with a markedly lower incidence of subsequent abnormality than their absence. In the case of spontaneous rupture of membranes and motor abnormality, the effect appeared to be non-linear, in that ruptured membranes appeared advantageous to the very lowest birthweight category, and possibly somewhat disadvantageous in the higher weight category.

Tab. X displays those variables ascertained by stepwise discriminant analysis from the factors in Tabs. V–VII to have had the most prodigious association with outcome. In the case of motor deficits, the presence of meconium and a rapid vaginal delivery were found to have the most

Tab. VII. Variables selected for subsequent analysis

Total score	
Parity (*)	(–) HBP – labor
Abruptio	(–) Creatinine clearance
Rapid delivery (*)	Hypocalcemia
Labor intolerance	Hypoglycemia
Meconium (*)	Patent ductus arteriosus
(Spontaneous ruptured membranes)	Seizures
	Anomaly
(Maternal age)	Resp. distress
(Race)	M Index (*)
(GA by dates)	SGA by exam
(–) HBP – 3rd TM	Hypotension
(–) HBP – PP	R/O sepsis

( ) = added for interest; significant in other categories; (–) = removed for inadequate numbers; (*) = statistically significant (at 0.05).

significant association, and 63.3% of all outcomes could be explained utilizing these two variables alone. None of the many other variables achieved statistical relevance (F to enter = 4.00) when the variables cited were removed.

Mental abnormalities were found curiously to correlate inversely with the demonstration of hypocalcemia on one or more determinations. Patients with demonstrated hypocalcemia had a markedly reduced incidence of mental handicap as opposed to those without. Birthweight as a continuous variable was found to have a rather linear inverse association with mental handicap, those of higher birthweights having progressively lower incidences of mental handicaps than those in the very lowest birthweight category. Combining these two considerations, 79.5% of outcomes could be correctly predicted.

When the overall subjective score was reviewed for associations with perinatal events, the presence of meconium was found to be a significant finding. By stepwise discriminant methodology, labor intolerance (as manifested by electronic fetal monitoring signs of fetal distress), when combined with meconium staining, predicted 78.5% of outcomes ($p = 0.017$). Curiously, labor intolerance was associated with a lower incidence of handicap.

Tab. VIII. Antepartum factors seeming to be of important in two or more areas

Mental	Motor	Score
Meconium	Meconium	Meconium
Advanced maternal age	Advanced maternal age	
Chicano race	Chicano race	
Spontaneous ruptured membranes (+)	Spontaneous ruptured membranes (?)	
GA by dates	GA by dates (+)	
Labor intolerance	Labor intolerance	
	Abruptio (+)	Abruptio (+)
	Rapid delivery (*)	Rapid delivery
	Advanced parity	Advanced parity

(+) = seems to confer advantage; (*) = disadvantage statistically significant; (?) = non-linear effect by birthweight.

Tab. IX. Neonatal factors seeming to be of importance in two or more areas

Mental	Motor	Score
Resp. distress	Resp. distress	Resp. distress
Hypocalcemia (+)	Hypocalcemia (+)	Hypocalcemia (+)
Patent ductus arteriosus (+)	Patent ductus arteriosus (+)	Patent ductus arteriosus (+)
Hypotension	Hypotension	Hypotension
M Index		M Index
Anomaly		Anomaly
R/O sepsis (+)		R/O sepsis (+)
	Hypoglycemia	Hypoglycemia

(+) = seems to confer some advantage; in the case of patent ductus, advantage is nullified if ligation required.

Tab. X. Variables found most likely to explain deficit – with % explained (stepwise discriminant analysis)

Deficit	Variable	F to enter*	% abnormal without parameter	% abnormal with parameter	% explained with variables combined
Motor	Meconium	13.985	33/76 = 43.4	5/6 = 100	
	Rapid delivery	6.157	31/73 = 42.5	7/8 = 87.5	
					63.3
Mental	Hypocalcemia	6.781	13/41 = 31.7	5/38 = 13.2	
	Birthweight (continuous variable)	8.222			
					79.5
Score	Labor intolerance	4.403	11/39 = 28.2	4/21 = 19.0	
	Meconium	13.699	13/55 = 23.6	4/5 = 80	
					78.5 (p = 0.017)

* shown in order of selection by the analysis system.

3 Comment

If one takes cognizance of the fact that all babies studied weighed less than 1500 gm at birth, the presence of meconium staining may be interpreted as a highly unusual finding. Its presence also suggests the possible influence of growth-retarded babies of more advanced gestational age than birthweight would indicate. If one refers to Tab. IV, however, it becomes readily apparent that the factor of small-for-gestational-age (lowest 10th percentile of birthweight for gestational age) was included as a variable, and did not emerge as a statistically significant category. Meconium staining was noted in 12 instances, with a 58% mortality and an 80% neurologic morbidity rate among survivors. Only 6/12 babies with this finding were SGA.

Rapid or precipitate delivery, (defined for this study as an unexpectedly brief late first and second stage of labor) has long been suspected of increasing the risk of trauma to the brain of the small premature baby. It is likely that this may explain its association with motor deficits. Likewise, the presence of meconium suggests the possibility of hypoxic brain injury, occurring either de novo or superimposed upon a fragile brain state predating labor. The association between labor intolerance (fetal distress) and a lower incidence of handicap may have resulted from a more aggressive interventionist policy in babies at recognized risk. This question cannot be resolved with certainty in a retrospective study.

The most inscrutable outcome of this very detailed analysis is the apparent "beneficial" effect of hypocalcemia upon subsequent neuorologic function. One can speculate that hypocalcemia, perhaps reflecting more responsive neonatal parathyroid activity, might be a sign of relative health, while its absence might be a manifestation of relative endocrinologic immaturity. It is also possible that hyperventilation and relative alkalosis secondary to aggressive support may have resulted in hypocalcemia through a reduction in the ionized calcium fraction, thereby representing indirect evidence of aggressive ventilatory support. There is no proof for any of the above speculations discoverable by retrospective analysis methods.

A third explanation for all of these outcomes is that one or more of these factors might have achieved statistical significance by chance alone, due to the large number of variables considered. It would be entirely possible that such chance association would be represented here, expect for the rather surprisingly high percentage of outcomes explainable by the very limited number of variables identified. Variables selected by stepwise discriminant analysis for these outcomes readily achieved significance without involving the host of additional factors subjected to analysis. It is therefore felt that these events discovered have a meaningful relationship to the ultimate observations of deficit.

No further attempt will be made in this presentation to speculate upon the significance of the

variables discovered, nor the lack of significance of the panorama of other variables considered, except to point out that some babies within this very low birthweight category died in the neonatal period. What are reported are the apparent influences of perinatal factors upon deficits among survivors. Factors contributing significantly to demise (perhaps the ultimate deficit) such as birthweight, gestational age, significant respiratory distress, premature labor, abruptio placentae, and other factors have been dealt with in prior reports [1, 2].

It is concluded that meconium staining, though a comparatively rare event in this birthweight group, is an ominous observation. Rapid delivery may predispose to injury, though mechanisms for this injury are unproven. Hypocalcemia appears associated with a better outcome than its absence, as is fetal distress. The reasons for these findings are unknown.

Summary

78 babies weighing less than 1500 gm at birth, surviving the neonatal period and available for follow-up, were studied. Data pertaining to perinatal events previously reported were correlated with neurological outcome over a 6–30 month period of evaluation. Motor abnormalities were found to correlate with the presence of meconium and the occurrence of rapid delivery. Mental handicap correlated inversely with hypocalcemia and birthweight. Overall score correlated with meconium and inversely with labor intolerance. These events were the only ones of a host of factors discovered by stepwise discriminant analysis among many maternal-fetal and neonatal variables. The importance of these observations is speculative.

Keywords: Follow-up, neonatal, perinatal, prematurity.

Zusammenfassung

Zur Bedeutung einiger ausgewählter Komplikationen in der Perinatalphase für die spätere Entwicklung von Kindern mit niedrigem Geburtsgewicht. III. Nachuntersuchungen

Wir beobachteten in einer Nachuntersuchung 78 Kinder mit einem Geburtsgewicht unter 1500 Gramm, die die Neugeborenenperiode überlebten. Dabei wurden Komplikationen, die in der perinatalen Phase aufgetreten und dokumentiert waren, mit der neurologischen Entwicklung über einen Beobachtungszeitraum von 6–30 Monaten korreliert. Motorische Entwicklungsverzögerungen traten gehäuft nach mekoniumhaltigem Fruchtwasser und einer kurzen Geburtsdauer auf. Eine mentale Beeinträchtigung war um so ausgeprägter, je niedriger das Geburtsgewicht war. Nach Hypocalcämien trat sie zu unserer Überraschung weniger gehäuft auf. Motorische und mentale Verzögerungen korrelierten positiv mit mekoniumhaltigem Fruchtwasser in der Anamnese und negativ mit der Wehenintoleranz. Es wurden nur einige perinatale Komplikationen aus einer Fülle von Beobachtungen herausgegriffen, die man durch eine schrittweise Diskriminationsanalyse der maternal-fetalen und neonatalen Variablen aufstellen kann. Die Bedeutung dieser Beobachtungen ist rein spekulativ.

Schlüsselwörter: Frühgeburt, Nachuntersuchung, Neonatalperiode, Perinatalphase.

Résumé

Signification néonatale des données périnatales sélectionnées chez les enfants de faible poids de naissance. III – Etudes de la surveillance

On a étudié 78 enfants pesant moins de 1500 g à la naissance; ayant survécu à la période néonatale et ayant pu être suivis de près. Les données appartenant aux événements périnataux rapportés antérieurement ont été corrélées avec le devenir neurologique sur une période d'évaluation de 6 à 30 mois. On a trouvé que les anomalies motrices sont corrélées avec la présence de méconium et l'existence d'un accouchement rapide. Les handicaps mentaux sont inversement corrélés avec l'hypocalcémie et le poids de naissance. Le score global est corrélé avec la mauvaise tolérance du travail. Ces éléments sont les seuls parmi une foule de facteurs mis en évidence par une analyse discriminative rigoureuse des nombreuses variables materno-fœtales et néonatales. L'importance de ces observations est spéculative.

Mots-clés: Néonatal, périnatal, prématurité, suivi.

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